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ORIGINAL REPORT

Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem-Cell Transplantation for Patients With Myelodysplastic Syndrome: A Prospective Randomized Phase III Study of the EBMT (RICMAC Trial)

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ABSTRACT

Purpose
To compare a reduced-intensity conditioning regimen (RIC) with a myeloablative conditioning regimen (MAC) before allogeneic transplantation in patients with myelodysplastic syndrome (MDS) within a randomized trial.

Patients and Methods
Within the European Society of Blood and Marrow Transplantation, we conducted a prospective, multicenter, open-label, randomized phase III trial that compared a busulfan-based RIC with MAC in patients with MDS or secondary acute myeloid leukemia. A total of 129 patients were enrolled from 18 centers. Patients were randomly assigned in a 1:1 ratio and were stratified according to donor, age, and blast count.

Results
Engraftment was comparable between both groups. The CI of acute graft-versus-host disease II to IV was 32.3% after RIC and 37.5% after MAC (P = .35). The CI of chronic graft-versus-host disease was 61.6% after RIC and 64.7% after MAC (P = .76). The CI of nonrelapse mortality after 1 year was 17% (95% CI, 8% to 26%) after RIC and 25% (95% CI, 15% to 36%) after MAC (P = .29). The CI of relapse at 2 years was 17% (95% CI, 8% to 26%) after RIC and 15% (95% CI, 6% to 24%) after MAC (P = .6), which resulted in a 2-year relapse-free survival and overall survival of 62% (95% CI, 50% to 74%) and 76% (95% CI, 66% to 87%), respectively, after RIC, and 58% (95% CI, 46% to 71%) and 63% (95% CI, 51% to 75%), respectively, after MAC (P = .58 and P = .08, respectively).

Conclusion
This prospective, randomized trial of the European Society of Blood and Marrow Transplantation provides evidence that RIC resulted in at least a 2-year relapse-free survival and overall survival similar to MAC in patients with MDS or secondary acute myeloid leukemia.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic disorders that are characterized by abnormal cellular maturation that results in cytopenias and variable risk of progression to acute leukemia.[1] Recently, new insights into the biology of this disease have helped to understand its pathophysiology, and new drugs, such as hypomethylating agents, have been shown to prolong survival[2]; however, allogeneic stem-cell transplantation from HLA-compatible donors is still the treatment with the highest chance of cure, and the number of transplantations is steadily increasing, especially in older patients.[3-6] This is primarily a result of increasing donor availability and the introduction of reduced-intensity conditioning regimens (RICs).[7] Several retrospective studies from the European Group of Blood and Marrow Transplantation (EBMT) as well as larger centers have reported a higher risk of relapse but a lower rate of nonrelapse mortality (NRM) when comparing RIC with myeloablative conditioning regimens (MACs), which has resulted in comparable

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survival after both approaches.[8-10] However, in all studies, the patient age was significantly higher in the RIC arm and smaller studies reported no difference in relapse rate if patients underwent transplantation in complete remission without active disease.[11]

To circumvent selection bias, we performed a prospective, multicenter, open-label phase III study comparing a busulfan-based standard myeloablative conditioning regimen with a busulfan-based RIC regimen in patients with MDS or secondary acute myeloid leukemia (sAML) and < 20% blasts (RICMAC Study).

PATIENTS AND METHODS

Patient Characteristics

In this prospective, multicenter, open-label randomized phase III study, patients were randomly assigned to receive a myeloablative conditioning regimen that consisted of busulfan (16 mg/kg orally or 12.8 mg/kg intravenously) and cyclophosphamide (120 mg/kg) or a an RIC regimen that consisted of busulfan (8 mg/kg orally or 6.4 mg/kg intravenously) and fludarabine (150 mg/m^2) followed by allogeneic stem-cell transplantation from a related or unrelated donor. Detailed characteristics of patients are listed in Table 1.

Major inclusion criteria were cytologically proven MDS and sAML with < 20% of blasts at time of transplantation, a matched related or unrelated donor (one mismatch was allowed), age 18 to 60 years for unrelated donors and age 50 to 65 years for related donors, which was amended in 02/2006 to age 18 to 65 years. Eighty-five percent of chemotherapies before transplantation were administered in advanced MDS (chronic myelomonocytic leukemia, refractory anemia with excess of blasts, and sAML) to reduce the number of blasts (85%), whereas only 15% of chemotherapies were administered to less advanced MDS (refractory anemia, refractory anemia with ringsideroblasts, and refractory anemia with multilineage dysplasia). Other inclusion criteria were adequate hepatic, renal, pulmonary, and cardiac functions. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and a short course of methotrexate (10 mg/m^2 on days +1, +3, +6, and +11) for both arms. In the case of unrelated donor antilymphocyte globulin (Fresenius, Graefelfing, Germany) at a cumulative does of 30 to 60 mg/kg or antithymocyte globulin (Thymoglobulin; Sanofi, Paris, France) at a cumulative dose of 6 to 10 mg/kg could be administered divided on days −3, −2, and −1 or alemtuzumab 100 mg divided on days −8 to −4 according to center policy; however, alemtuzumab was not used in a single patient.

Supportive Care

Cyclosporine A dose was adjusted to a whole-blood level between 200 and 300 μg/L and should be tapered from day +120 to be discontinued at day +180. All patients received fluconazole or other antifungal prophylaxis according to local policy. Antibacterial prophylaxis consisted of ofloxacin or ciprofloxacin and antiviral prophylaxis of acyclovir. Cytomegalovirus (CMV) reactivation was treated pre-emptively with ganciclovir or foscarnet. Further anti-infective prophylaxis consisted of twice weekly cotrimoxazole or monthly inhalation with pentamidine. Blood products were administered according to local policy. Epstein-Barr virus reactivation was defined as positive DNA assay on whole blood or plasma, according to center policy. CMV reactivation was defined as positive CMV pp65 antigenemia and/or DNA assay.

The primary end point of the study was NRM after 1 year. Secondary end points were comparison of engraftment, toxicity, acute and chronic GVHD, infectious complications, and event-free survival and overall survival at 2 years.

Acute GVHD was scored according to Glucksberg,[12] whereas chronic GVHD was scored according to Shulman criteria (limited and extensive).[13]

The RICMAC Study was conducted in accordance with good clinical practice guidelines and the provisions of the Declaration of Helsinki. Protocol

Table 1. Patient Characteristics

Characteristic	Standard Conditioning, No. (n = 64)	Reduced-Intensity Conditioning, No. (n = 65)	P
Age, years			.874
Median (range)	50 (19-64)	51 (22-63)	
≤ 45	15	15	
46-50	17	16	
51-55	10	17	
56-60	19	13	
61-65	3	4	
Diagnosis according to WHO			.569*
5q	0	2	
CMML	3	3	
MDS unclassifiable	2	3	
RA	4	3	
RARS	5	3	
RAEB-1	12	19	
RAEB-2	15	17	
RCMD	12	8	
RCMD-RS	1	3	
sAML	8	4	
Missing	2		
Prior induction chemotherapy			.253
No	33	40	
Yes	31	25	
Donor			.962
Matched related	17	16	
Matched unrelated	36	38	
Mismatch unrelated/ related	11	11	
ATG as GVHD prophylaxis			.791
No	31	33	
Yes	33	32	
Blasts at transplantation			.034
Median (range)	4% (0-18)	5% (0-18)	
> 5%	18	30	
≤ 5%	46	35	
Recipient sex			.916
Male	38	8	
Female	26	27	
Donor sex			.846
Male	40	43	
Female	22	22	
Missing	2		
Gender mismatch			.285
Male/female	9	14	
Others	53	51	
Missing	2		
Recipient/donor CMV constellation			.250
Negative/negative	28	21	
Positive/negative	12	9	
Negative/positive	10	9	
Positive/positive	14	24	
Missing		2	
IPSS at diagnosis			.737*
Low risk	2		
Intermediate I	28	25	
Intermediate II	18	24	
High risk	9	7	
Missing	7	7	
Cytogenetic risk			.650
Low	24	28	
Intermediate	17	13	
High	17	18	
Missing	6	6	

(continued on following page)

Table 1. Patient Characteristics (continued)

Characteristic	Standard Conditioning, No. (n = 64)	Reduced-Intensity Conditioning, No. (n = 65)	*P*
ECOG performance status at diagnosis			.692*
0	18	21	
1	32	29	
2	3	3	
3	0	2	
Missing	11	10	
Busulfan			.053
Intravenously	47	38	
Orally	16	27	
Missing	1	0	
Stem cell source			.311
Bone marrow	3	6	
PBSC	61	59	

Abbreviations: ATG, antilymphocyte globulin; CMML, chronic myelomonocytic leukemia; CMV, cytomegalovirus; ECOG, Eastern Cooperative Oncology Group; GVHD, graft-versus-host disease; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; PBSC, peripheral blood stem cell; RA, refractory anemia; RAEB, refractory anemia with excess of blasts; RARS, refractory anemia with ringsideroblasts; RCMD, refractory anemia with multilineage dysplasia; sAML, secondary acute myeloid leukemia.
*Diagnosis: RAEB-1/RAEB-2/sAML/CMML *v* other; IPSS at diagnosis: low-intermedia I *v* intermediate II *v* high; ECOG performance status, 0 *v* 1-3.

approval was obtained from an independent ethics committee at each study site. All patients provided written informed consent. EBMT sponsored the study.

Statistical Methods

The study planned to enroll 160 patients to detect a difference in 1-year treatment-related mortality of 40% after MAC versus 20% after RIC with a power of 90% and a significance level of 5% in a two-sided test using a proportional hazards model. As a result of a slow accrual rate, inclusion stopped when 129 patients were enrolled. At that moment, a blinded power calculation on the basis of the same hypotheses on expected NRM rates and in various likely scenarios for relapse rate returned power superior to 80% with a sample size of 120 patients. It was thus considered appropriate to stop the accrual and proceed with the final analysis. This showed, however, actual NRM rates lower than expected, in particular, in the MAC arm; thus, the study was underpowered (< 35%) to detect a true difference in NRM that was equal to the observed difference.

Therapy-related mortality—NRM— and relapse were analyzed in a competing risks framework by using the cumulative incidence estimator and the Gray test for univariable analysis as well as Cox proportional hazards regression for analysis of cause-specific hazards. Overall survival and relapse-free survival were estimated by using the Kaplan-Meier method and compared with the Log-Rank test in univariable analysis, and by Cox proportional hazards regression in multivariable analysis. Stratification factors (donor type, blasts, age) as well as patient and donor gender or gender mismatch, CMV status combination, diagnosis subgroup (sAML *v* other), cytogenetics, International Prognostic Scoring System score, performance status, prior chemotherapy, and use of busulfan were considered for inclusion in Cox models with the random assignment arm. Selection was done on the basis of significance, taking into account prior clinical knowledge, the presence of missing values, and aspects related to model validation. Cases with missing values for one variable were excluded, but we confirmed the robustness of the results when including the missing variable as a further level. The proportional hazards assumption in Cox models was assessed by analysis of scaled Schoenfeld residuals, and no relevant departure was detected. The study was not specifically powered to investigate interactions and perform subgroup analyses. Following protocol, subgroup analyses were performed when the corresponding interaction term with the random assignment arm was found to be significant at the 10% level in the Cox proportional hazards regression model.

Acute and chronic GVHD were assessed by using the crude cumulative incidence estimator and the Gray test considering relapse and death as competing risks. Incidences of infections were estimated in terms of rates (for 100 person-years), and a Poisson-based exact method was used for testing rate ratios. Occurrence of serious adverse events as well as categorical characteristics were compared by χ^2 or Fisher's exact test, and the Mann-Whitney test was used for continuous variables.

All end points were analyzed including all randomly assigned patients grouped according to random assignment arm, except secondary safety end points, which were analyzed in the subpopulation of patients who were treated according to protocol (n = 125; Fig 1). Following study protocol that required a follow-up of 2 years, all end points were artificially censored at 24 months. Curves are not displayed beyond this time because only a minority of patients had longer follow-up.

Analyses were performed by using SPSS for Windows version 23 (SPSS, Chicago, IL) and R package version 3.1.0 (The R Foundation, Vienna, Austria; libraries survival, prodlim, cmprsk, and exactci).

Random Assignment Procedure

Patients were randomly assigned in a 1:1 ratio and stratified according to donor (related *v* unrelated) blasts (< 5% or > 5%) and age (< 45 years or > 45 years). Patient flow is shown in Fig 2.

RESULTS

Patients and Treatment

Between May 2004 and December 2012, a total of 129 patients were enrolled in 18 centers and seven countries. Baseline characteristics of the remaining 129 patients were well balanced (Table 1).

Graft Failure and Engraftment

Four and three graft failures occurred after standard and RIC regimens, respectively (P = .72). Median time for leukocyte engraftment (absolute neutrophil count $\geq 0.5 \times 10^9$/L) was 15 days in each arm, and for platelet ($\geq 50 \times 10^9$/L) engraftment, 15 days (range, 4 to 158 days) in the RIC arm versus 16 days (range, 10 to 185 days) in the standard arm (P = .33; Table 2).

Acute and Chronic GVHD

Cumulative incidence of acute GVHD grade II to IV and grade III and IV was 32.3% and 15% in the RIC arm, respectively, and 37.5% and 14% in the standard arm, respectively (P = .35; Table 2). The CI of chronic GVHD at 24 months was 61.6% (95% CI, 48.9% to 74.3%) in the RIC arm and 64.7% (95% CI, 51.3% to 78.1%) in the standard arm (P = .76).

Toxicity and NRM

Infectious complications were more frequently observed in the standard arm (rate in 100 patient-years at day 100, 6.9 *v* 4.3; P = .002). There was no difference in CMV reactivation, EBV reactivation, or other viral or fungal infection (Table 2). Veno-occlusive disease was reported in four patients in the MAC arm and no patients in the RIC arm, but no patient died of veno-occlusive disease. NRMs at 1 year was 16.9% (95% CI, 7.8% to 26.0%) in the RIC arm and 25.3% (95% CI, 14.6% to 36%) in the standard arm (P = .29; Table 2 and Fig 2A).

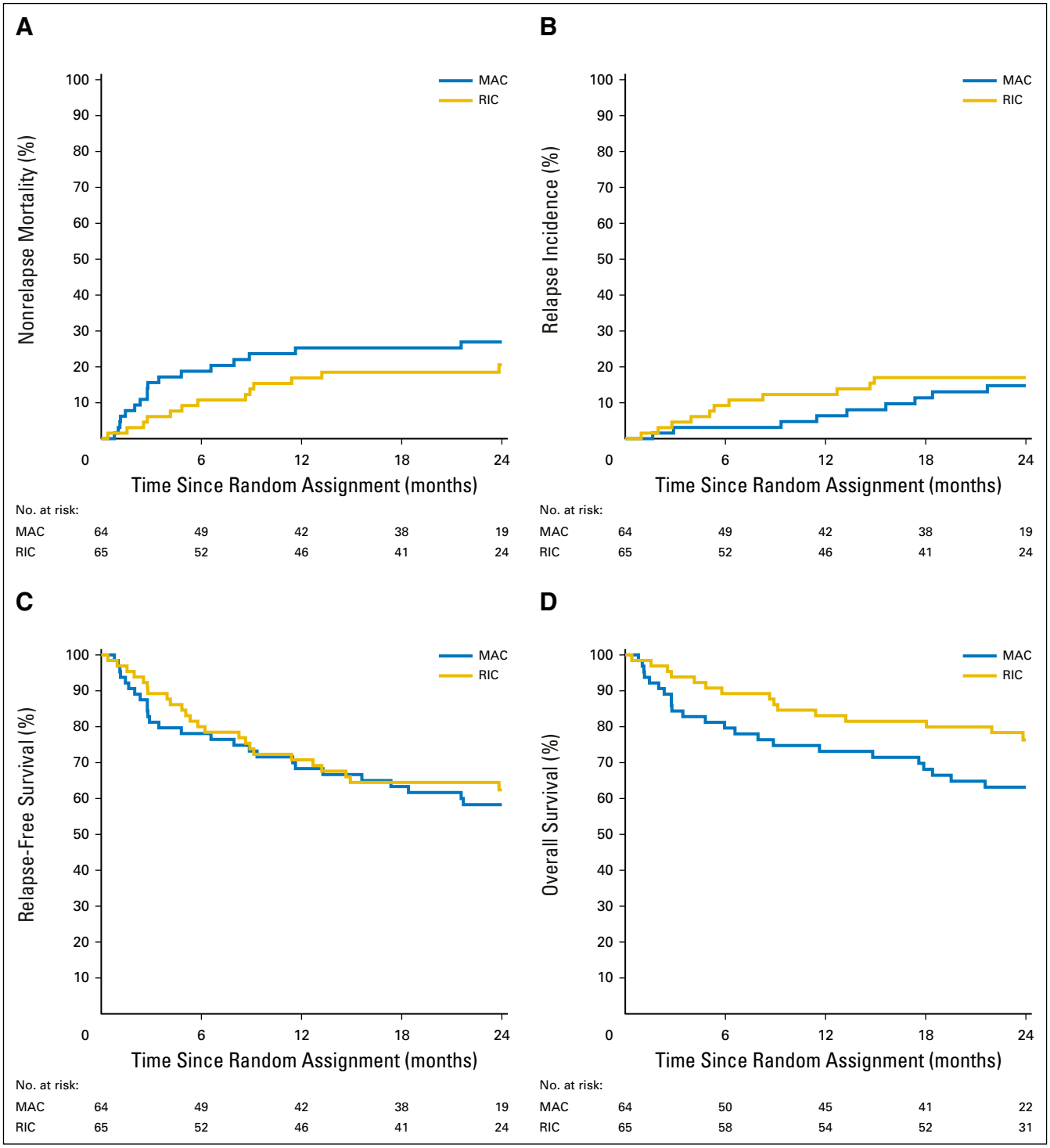

Fig 1. (A–D) Nonrelapse mortality (A), relapse incidence (B), relapse-free survival (C), and overall survival (D) according to intensity of conditioning regimen. MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.

Organ toxicity according to Bearman's score did not differ, apart from stomatitis, which was significantly lower in the RIC arm (P = .05; Appendix Tables A1 and A2, online only)

Relapse

The CI of relapse at 2 years was 17.0% (95% CI, 7.9% to 26.2%) in the RIC arm and 14.8% (95% CI, 5.8% to 23.7%) in the standard arm (P = .64; Table 2 and Fig 2B).

Survival

The 2-year relapse-free survival was 62.4% (95% CI, 50.4% to 74.4%) in the RIC arm and 58.3% (95% CI, 46.0% to 70.6%) in the standard arm (P = .58), and 2-year overall survival was 76.3% (95% CI, 65.8% to 86.9%) after RIC versus 63.2% (95% CI, 51.1% to 75.2%) after standard conditioning, respectively (P = .08; Table 2 and Figs 2C and 2D).

Table 2. Results

	Standard Conditioning	Reduced-Intensity Conditioning	*P*
Graft failure	4	3	.72
Median time for leukocytes > 1.0 × 10^9/L (range), days	15 (9-32)	15 (4-25)	.81
Median time for platelets > 50 × 10^9/L (range), days	16 (10-185)	15 (4-158)	.33
Acute GVHD, No. (%)			.35
Grade 1	8 (13)	13 (20)	
Grade 2	15 (23)	11 (17)	
Grade 3	6 (9)	9 (14)	
Grade 4	3 (5)	1 (1)	
Chronic GVHD, No. (%)			.76
Limited	11 (22)	13 (23)	
Extensive	21 (41)	25 (44)	
Overall No. of infections	48	44	
Rate (per 100 person-years) day 1-100	6.9 (5.7-8.4)	4.3 (3.4-5.4)	.002
Rate (per 100 person-years) total follow-up	2.0 (1.7-2.3)	1.4 (1.2-1.6)	.002
Overall No. of bacterial infections	31	22	
Rate (per 100 person-years) day 1-100	2.3 (1.6-3.2)	1.3 (0.8-1.9)	.029
Rate (per 100 person-years) total follow-up	0.6 (0.4-0.8)	0.4 (0.3-0.5)	.133
Overall No. of CMV reactivation, No.	12	18	.17
Overall No. of EBV reactivation, No.	8	11	.49
Overall No. of viral infections, No.	21	14	.24
No. of bacterial infections until day 100, No.	28	17	.03
Number of fungal infections until day 100, No.	11	8	.53
Nonrelapse mortality at 1 year, % (95% CI)	25.3 (14.6 to 36.0)	16.9 (7.8 to 26.0)	.29
Relapse incidence at 2 years, % (95% CI)	14.8 (5.8 to 23.7)	17.0 (7.9 to 26.2)	.64
Relapse-free survival at 2 years, % (95% CI)	58.3 (46.0 to 70.6)	62.4 (50.4 to 74.4)	.58
Overall survival at 2 years, % (95% CI)	63.2 (51.1 to 75.2)	76.3 (65.8 to 86.9)	.08
Cause of death			.18
Disease related	5	2	
Transplant related	18	11	
Other	0	2	

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; GVHD, graft-versus-host disease.

Multivariable and Subgroup Analyses

In a multivariable analysis (MVA), NRM was influenced by performance status (Eastern Cooperative Oncology Group performance status > 0: hazard ratio [HR], 3.68; 95% CI, 1.26 to 10.76; *P* = .02) and cytogenetic risk (HR low *v* intermediate, 5.63; 95% CI, 1.28 to 24.82; *P* = .02; HR high *v* intermediate, 4.28; 95% CI, 0.91 to 20.19; *P* = .07), whereas for RIC, only a trend for lower NRM was noted (HR, 0.63; 95% CI, 0.28 to 1.40; *P* = .26; Table 3). In the model of NRM, an interaction was found between the random assignment arm and cytogenetics (*P* = .08), which led to a subgroup analysis stratified by cytogenetics risk group. In the low-risk group, the RIC arm resulted in lower NRM (HR, 0.30; 95% CI, 0.10 to 0.89; *P* = .03). In the intermediate- and high-risk cytogenetic groups, RIC resulted in a higher NRM (HR, 1.17; 95% CI, 0.07 to 18.83; *P* = .9; and HR, 2.14; 95% CI, 0.51 to 9.00; *P* = .3, respectively). A conclusive answer for this observation cannot be given, but a possible explanation would be that low-risk patients are protected from relapse and are thus more at risk for death without relapse. No other interaction was found.

In an MVA for relapse, advanced disease resulted in a higher risk (HR, 13.26; 95% CI, 1.77 to 99.14; *P* = .01), whereas RIC had an HR of only 1.05 (95% CI, 0.44 to 2.54; *P* = .9). Advanced disease was also a significant risk factor for lower relapse-free survival (HR, 2.77; 95% CI, 1.30 to 5.91; *P* = .008), whereas RIC was not (HR, 1.05; 95% CI, 0.44 to 2.54; *P* = .9). In an MVA for overall survival, worse survival was noted for low versus intermediate cytogenetic risk (HR, 6.06; 95% CI, 1.69 to 21.80; *P* = .005), for high versus intermediate cytogenetic risk (HR, 4.51; 95% CI, 1.28 to 15.86; *P* = .02), and for advanced disease (HR, 2.26; 95% CI, 0.95 to 5.39; *P* = .06), whereas RIC resulted in improved overall survival (HR, 0.41; 95% CI, 0.19 to 0.87; *P* = .02).

DISCUSSION

In this prospective, multicenter, multinational phase III study of the EBMT RIC regimen, administration before allogeneic stem-cell transplantation in patients with MDS was at least equivalent to the results after treatment with a standard myeloablative conditioning regimen. The CI of relapse at 2 years was nearly identical independent of conditioning regimen intensity, whereas NRM tended to be higher after myeloablative conditioning, although not significantly. The only risk factor for relapse in a multivariable analysis was advanced disease status, which was defined as CMML, RAEB, or sAML.

The role of conditioning regimen intensity before allogeneic stem-cell transplantation for MDS has not been studied prospectively and recommendations are based on retrospective single-center or registry studies.[8,10] Despite this lack of evidence, the European Leukemia Net recommended a standard myeloablative

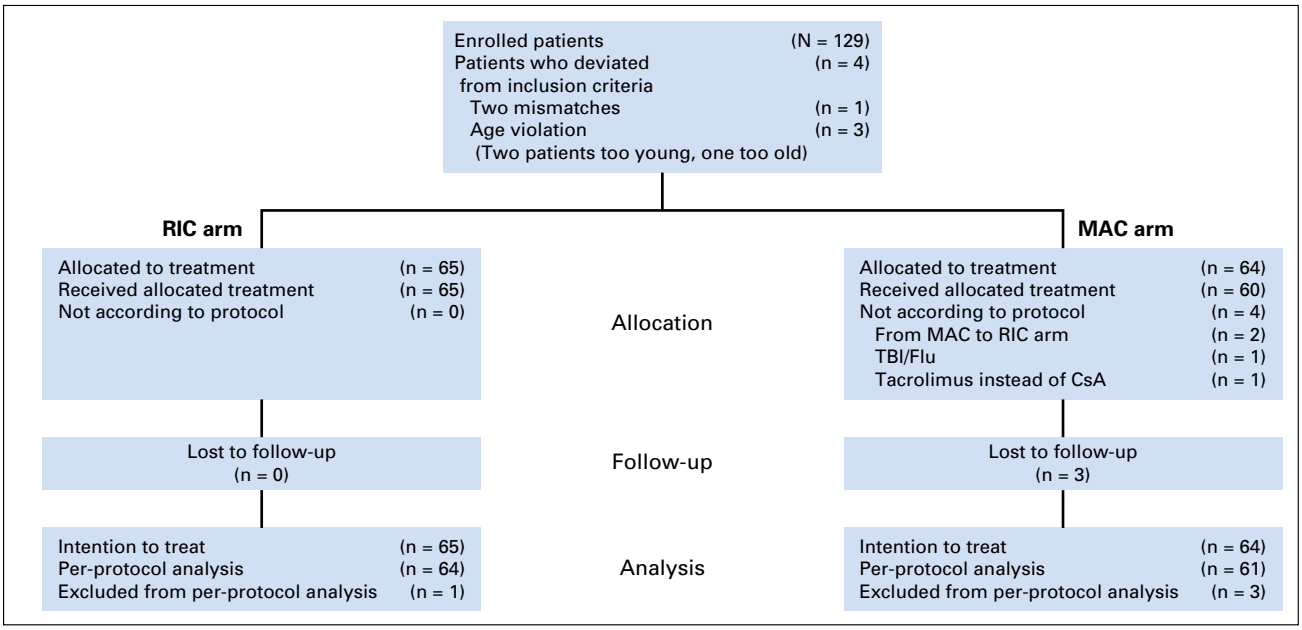

Fig 2. Flow diagram of the study. Four patients deviated from the inclusion criteria: one patient had two mismatches in HLA between patient and donor, one patient was too old, and two patients where too young. The lower level for age inclusion was amended during the recruitment phase from age 50 years to age 18 years—because of a competing European Group of Blood and Marrow Transplantation myelodysplastic syndrome trial, age inclusion for patients with related donor was restricted to age 50 to 65 years at first; when the competing trial stopped, age inclusion was amended. Both patients that were too young (age 43 and 48 years) at time of registration did fulfill these extended inclusion criteria; therefore, these two patients are included in both the intention-to-treat analysis as well as the per-protocol analysis. There are four patients who were excluded from the per-protocol analysis: The patient who was too old (this patient was treated with total body irradiation/fludarabine [TBI/Flu]). The patient who had two mismatches and the two patients who were treated with reduced-intensity conditioning (RIC) regimen in the myeloablative conditioning (MAC) arm. The patient who was treated with tacrolimus instead of cyclosporine A (CsA) was included in both the intention-to-treat analysis and the per protocol analysis.

conditioning regimen for all patients without comorbidities. Those patients with comorbidities should receive RIC, preferably within a clinical trial.[1] The rationale for using RIC before allogeneic stem-cell transplantation is to shift from high-dose chemotherapy that is aimed at maximizing cytotoxic leukemia killing to a more immune-mediated effect by harvesting the graft-versus-tumor effect to eradicate the disease. Retrospective registry studies have suggested a low risk of NRM but a higher risk of relapse after RIC; however, patients who received RIC were older than those who received standard myeloablative conditioning.[4,8] To avoid selection bias in the study, all patients should have been eligible for standard myeloablative conditioning at the time of study inclusion; however, enrollment in the study was rather slow, which may be a result of the strict inclusion criteria for age and also because of patients declining to be randomly assigned and physician concern, because several retrospective studies suggested a higher risk of relapse after RIC; therefore, selection bias cannot be excluded. RIC is thought to result in lower toxicity and lower mortality. Regarding toxicity, we noted only significantly less stomatitis, which resulted only in a trend for a lower NRM. Because mismatch unrelated donors were included in this study, the NRM of MAC was surprisingly low and the observed 25% NRM was much lower than the hypothesized 40% in the study protocol. A higher number of infections—mainly of bacterial origin—was observed after MAC conditioning. Another unexpected result was the higher NRM for the low-risk cytogenetic group compared with intermediate cytogenetic risk. In a nonpowered subanalysis for NRM, RIC in the low-risk group resulted in lower NRM. In the intermediate- and high-risk cytogenetic groups, RIC resulted in a higher but nonsignificant NRM. Our analysis is not conclusive regarding the role of RIC in the high-risk group. Advanced disease is a significant factor for relapse-free survival and overall survival, but our study protocol did not allow subgroup analyses if interaction was $P > .1$.

In a multivariate analysis for overall survival, RIC resulted in a significant survival benefit at 2 years. Improved survival after RIC might be a result of lower mortality after relapse. Whereas after MAC six of nine patients who experienced relapse died, in the RIC arm, only two of 11 patients who experienced relapse died.

Whereas retrospective studies suggest a higher risk of relapse but a lower NRM after RIC, there are few available prospective studies that show similar survival rates. These studies, however, included mainly or only patients with AML who may differ in outcome from patients with MDS. In a German multicenter study, patients with AML in 1. Complete remission reduced-intensity total body irradiation–based conditioning regimen resulted in no significant difference in NRM, relapse incidence, and disease-free survival and overall survival compared with a standard myeloablative conditioning regimen.[14]

In older patients with AML who were in remission, a busulfan-based RIC regimen resulted in a lower NRM but similar overall survival.[15] These trials, however, included only patients with AML. A recent multicenter US trial that compared RIC versus myeloablative conditioning and that included patients with AML and MDS was closed prematurely because of inferior outcome after RIC (BMT-CTN 0901 trial); however, the superior effect for survival of myeloablative conditioning was seen observed in patients with AML but not in those with MDS.[16] Whereas in recent years the

Table 3. Multivariable Analysis

Parameter	HR (95% CI)	*P*
Nonrelapse mortality		
RIC	0.63 (0.28 to 1.40)	.26
Cytogenetics		.02
Low risk	5.63 (1.28 to 24.82)	.02
High risk	4.28 (0.91 to 20.19)	.07
ECOG > 0	3.68 (1.26 to 10.76)	.02
Relapse		
RIC	1.05 (0.44 to 2.54)	.91
Advanced disease	13.26(1.77 to 99.14)	.01
Relapse-free survival		
RIC	0.76 (0.42 to 1.38)	.36
Advanced disease	2.77 (1.30 to 5.91)	.008
Overall survival		
RIC	0.41 (0.19 to 0.87)	.02
Cytogenetics		< .001
Low risk	6.06 (1.69 to 21.80)	.005
High risk	4.51 (1.28 to 15.86)	.02
ECOG > 0	2.32 (0.99 to 5.43)	.05
Advanced disease	2.26 (0.95 to 5.39)	.06

NOTE. In the model of nonrelapse mortality (NRM), an interaction was found between the random assignment arm and cytogenetics ($P = .08$), which led to a subgroup analysis stratified by cytogenetics risk group. In the low-risk group, lower performance status (ECOG > 0: HR, 2.65; 95% CI, 0.74 to 9.47; $P = .13$) influenced NRM, whereas the RIC arm resulted in lower NRM (HR, 0.30; 95% CI, 0.10 to 0.89; $P = .03$). In the intermediate- and high-risk cytogenetic groups, RIC resulted in a higher NRM (HR, 1.17; 95% CI, 0.07 to 18.83; $P = .9$; and HR, 2.14; 95% CI, 0.51 to 9.00; $P = .3$, respectively).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; RIC, reduced-intensity conditioning.

number of allogeneic stem-cell transplantation for older patients with MDS have increased,[3] in our study, the majority of patients were age < 60 years, because the upper age limit in the study was age 60 years for unrelated donor and age 65 years for related donor.

In summary, our study shows that RIC and MAC followed by allogeneic stem-cell transplantation resulted in at least an equivalent survival trend for a better 2-year overall survival, especially in the cytogenetic low-risk group and can be offered as an alternative to a myeloablative regimen.

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Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem-Cell Transplantation for Patients With Myelodysplastic Syndrome: A Prospective Randomized Phase III Study of the EBMT (RICMAC Trial)

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Appendix

Table A1. Safety Statistics (per-protocol population)

Parameter	Random Assignment Arm		
	0 MAC, No. (%)	1 RIC, No. (%)	Total, No. (%)
max bearman			
0: no or grade 1	8 (17.0)	15 (32.6)	23 (24.7)
1: 2 or higher	39 (83.0)	31 (67.4)	70 (75.3)
Total	47 (100.0)	46 (100.0)	93 (100.0)
cardiac_grade			
.00: no or grade 1	43 (91.5)	44 (97.8)	87 (94.6)
1.00: 2 or higher	4 (8.5)	1 (2.2)	5 (5.4)
Total	47 (100.0)	45 (100.0)	92 (100.0)
bladder_grade			
.00: no or grade 1	46 (97.9)	45 (100.0)	91 (98.9)
1.00: 2 or higher	1 (2.1)	0 (0.0)	1 (1.1)
Total	47 (100.0)	45 (100.0)	92 (100.0)
renal_grade			
.00: no or grade 1	38 (80.9)	41 (91.1)	79 (85.9)
1.00: 2 or higher	9 (19.1)	4 (8.9)	13 (14.1)
Total	47 (100.0)	45 (100.0)	92 (100.0)
pulmonary_grade			
.00: no or grade 1	43 (91.5)	43 (95.6)	86 (93.5)
1.00: 2 or higher	4 (8.5)	2 (4.4)	6 (6.5)
Total	47 (100.0)	45 (100.0)	92 (100.0)
hepatic_grade			
.00: no or grade 1	36 (76.6)	38 (84.4)	74 (80.4)
1.00: 2 or higher	11 (23.4)	7 (15.6)	18 (19.6)
Total	47 (100.0)	45 (100.0)	92 (100.0)
cns_grade			
.00: no or grade 1	46 (97.9)	43 (95.6)	89 (96.7)
1.00: 2 or higher	1 (2.1)	2 (4.4)	3 (3.3)
Total	47 (100.0)	45 (100.0)	92 (100.0)
stomatitis_grade			
.00: no or grade 1	13 (27.7)	22 (48.9)	35 (38.0)
1.00: 2 or higher	34 (72.3)	23 (51.1)	57 (62.0)
Total	47 (100.0)	45 (100.0)	92 (100.0)
gi_grade			
.00: no or grade 1	46 (97.9)	43 (95.6)	89 (96.7)
1.00: 2 or higher	1 (2.1)	2 (4.4)	3 (3.3)
Total	47 (100.0)	45 (100.0)	92 (100.0)

NOTE. Bearman grades are recoded as 0 = no event or grade 1 *v* 1 = grade 2 or higher.

Table A2. Tests for Significance

Parameter	χ^2 Test	Fisher's Exact Test
max Bearman	0.082	0.097
cardiac_grade	0.184*	0.362
bladder_grade	0.325*†	1.000
renal_grade	0.158*	0.232
pulmonary_grade	0.430*	0.677
hepatic_grade	0.343	0.434
cns_grade	0.532*	0.613
stomatitis_grade	0.036	0.053
gi_grade	0.532*	0.613

NOTE. Because of the small numbers, the χ^2 test can be invalid, in which case Fisher's exact test is more appropriate.

*More than 20% of cells in this table have expected cell counts < 5. χ^2 results may be invalid.

†The minimum expected cell count in this table is < 1. χ^2 results may be invalid.